The Effect of Sudden Clozapine Discontinuation on Management of Schizophrenic Patients: A Retrospective Controlled Study

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Background: The aims of our study were (1) to compare the dose of clozapine needed to achieve remission in patients who stopped their treatment (study group) versus patients who continued taking this medication (control group) and (2) to compare the clinical characteristics of remission between these 2 groups.

Method: We retrospectively reviewed the medical records of all treatment-resistant schizophrenic and schizoaffective patients (according to DSM-IV criteria) who were treated with clozapine over a period of 9 years, from January 1995 through December 2003. The study group consisted of 43 patients and the control group of 12 patients. All patients' files from both groups were examined, and each patient's remission was scored twice—initially on discharge from the hospital and subsequently after final discharge for the study group, or at the end of the study for the control group.

Results: The change of clozapine dose from the first to the last remission expressed by percentage shows a significant difference between the 43% increase in clozapine dose in the study group and the 12.5% decrease in clozapine dose in the control group ($p < .001$). Quality of remission assessment showed deterioration in the global remission score in the study group, while the quality of remission assessment in the control group did not show any change.

Conclusions: Our findings suggest that the discontinuation of clozapine treatment leads to a deterioration in the quality of remission, with a need for an increased dose of clozapine. Further prospective studies on larger samples are needed to confirm these findings.

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Clozapine was the first novel antipsychotic drug and is still considered the most effective antipsychotic drug.[1] Clozapine is indicated as a treatment for treatment-resistant schizophrenic and schizoaffective patients.[2–5] There are reports regarding the beneficial effects of this drug on negative symptoms and its positive influence on information-processing in schizophrenia.[1,6–8]

It is a well-known fact that the major reason for psychotic exacerbations is sudden discontinuation of treatment, usually as an expression of noncompliance.[9,10] Due to significant clinical properties of clozapine, much effort has been expended in attempting to analyze the mode of its action, although it remains something of an enigma.[11] Risk of relapse after withdrawal of clozapine seems to be greater than after withdrawal of classic neuroleptics. Abrupt withdrawal from clozapine can be associated in some schizophrenic patients with rapid-onset "rebound psychosis."[12–19] The mechanism of this rebound phenomenon remains unclear at this time.

Some patients may become antipsychotic-resistant for at least several weeks after withdrawal. Therefore, it is recommended that clozapine therapy be discontinued slowly and gradually when necessary.[20]

Therapeutic tolerance, rebound psychosis, and supersensitivity psychosis have been reported with clozapine, olanzapine, and quetiapine.[12,18,21,22] Tolerance is defined as the need to increase the dose progressively in order to produce the effect originally achieved by smaller amounts of medication.[23] The effects of repeated drug treatment are of particular interest since the clinical effects of antipsychotics generally take several weeks to appear.[24]

Relapses of schizophrenic episodes, especially when more severe, have serious repercussions. The patient may lose his/her family, social contacts, occupation, or academic status. In addition, a relapse may cause deleterious effects on the personality, with a worsening of negative signs and a decrease in function.

Based on our clinical impressions and on reports from other clinicians,[13,16,17,19,20] we decided to examine the hypothesis that the abrupt discontinuation of clozapine treatment may have a negative influence on the quality of remission and result in the patient's requiring larger doses

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Table 1. Demographic and Clinical Characteristics of Patients

Characteristic	Study Group (N = 43)	Control Group (N = 12)	p
Age, y			NS
Range	27–51	24–57	
Mean ± SD	36.90 ± 1.53	39.75 ± 4.75	
Sex, N (%)			NS
Male	33 (76.7)	7 (58.3)	
Female	10 (23.3)	5 (41.7)	
Diagnosis, N (%)			NS
Schizophrenia	28 (65.1)	9 (75.0)	
Schizoaffective disorder	15 (34.9)	3 (25.0)	
Duration of illness, y			NS
Range	3–18	4–16	
Mean ± SD	11.6 ± 3.2	12.3 ± 4.1	

Abbreviation: NS = not significant.

of clozapine for remission. In order to examine this hypothesis, we retrospectively examined medical records of patients who had been treated with clozapine.

METHOD

We designed a comparative study of 2 groups of patients who were treated with clozapine. Both groups included schizophrenic and schizoaffective patients. The study group included patients who had abruptly ceased treatment, but their treatment was renewed upon hospitalization for acute rebound psychotic exacerbation, and subsequent remission was achieved. The control group included outpatients in remission who continued their treatment without interruption.

We retrospectively reviewed the medical records of all treatment-resistant schizophrenic and schizoaffective patients (according to criteria developed by Kane et al.[25]) who were treated in the Beer-Sheva Mental Health Center from January 1995 through December 2003. Of the 560 records that were screened, there were 108 patients who were treated with clozapine. Part of the remaining 452 patients were treated with either a combination of first- and second-generation antipsychotics or a combination of 2 second-generation antipsychotics. Another part of the remaining patients were not candidates for clozapine treatment since they were noncompliant to oral medications and were switched to long-acting neuroleptics or had contraindications for somatic reasons. Of the 108 patients treated with clozapine, 43 patients met the inclusion criteria for the study group and 12 patients were included as controls (Table 1). The remaining 53 patients were lost to follow-up.

In order to examine our hypothesis, we determined the criteria for inclusion of patients in the study group and control group. Inclusion criteria for the study were (1) treatment-resistant schizophrenic or schizoaffective patients, according to DSM-IV, who were treated and discharged into the community with clozapine, (2) patients who stopped taking clozapine abruptly (study group) or patients in remission who continued taking clozapine and continued outpatient clinic follow-up (control group), (3) the psychotic exacerbation required hospitalization, and (4) clozapine treatment was renewed. Patients with a history of drug or alcohol abuse were not included.

The study protocol was approved by the medical ethics board of our center, and the study was conducted in accordance with the Declaration of Helsinki.

Efficacy of treatment was determined by (1) the dose needed to achieve remission and (2) the quality of remission. In order to characterize the quality of remission, we designed a "remission assessment score" consisting of 3 factors: (1) functioning level, (2) positive symptoms, and (3) negative symptoms. This scoring system was based on a summary of these components; maximum possible score was 9, and minimum score 3. The evaluation of each patient was performed retrospectively by a single rater and was based on medical records.

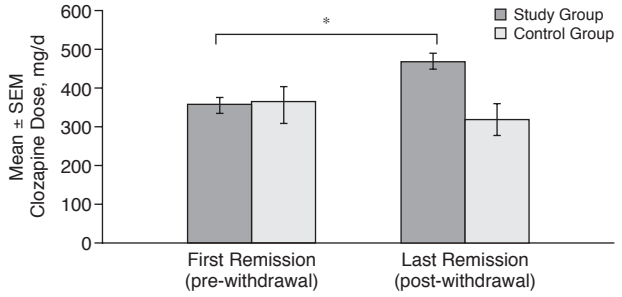
Every dimension of the remission assessment score was divided into 3 subgroups according to the severity of disturbance, as follows. Functioning level: severe disturbances in functioning level—patient is completely dependent (1 point); moderate disturbances in functioning level—patient is partially independent, needs help or observation (2 points); no disturbances in functioning level—patient is completely independent and returns to his/her previous life (3 points). Positive symptoms: florid positive symptoms that influence the patient's behavior (1 point); incomplete improvement—positive symptoms still remain but without influence on behavior (2 points); no positive symptoms (3 points). Negative symptoms: marked negative symptoms—inappropriate blunted affect, lack of motivation, poor hygiene, anhedonia, impaired judgment and insight (1 point); moderate negative symptoms (2 points); mild negative symptoms—restriction of affect (3 points).

All patients' files from both the study and control groups were examined and each patient was scored twice, based on the description in the files. The first assessment was made upon discharge from the hospital after initial remission with clozapine treatment. The second score was made after the last discharge for the study group and at the end of the study for the control group. All patients were evaluated according to the rating scales mentioned above for their functioning level and positive and negative symptoms. Each of these 3 baseline and endpoint measures of symptoms and function were compared separately and together. The mean value of change in clozapine dose for each patient from the first to last remission was calculated.

Statistical Analysis

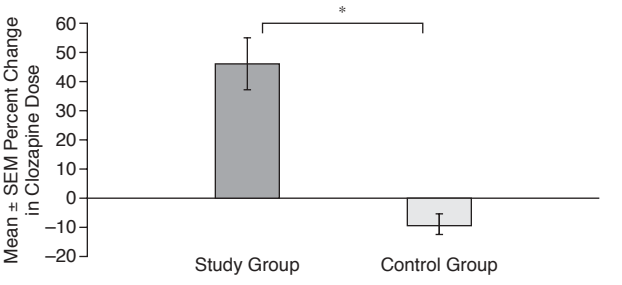
The statistical analyses were performed using the t test. Proportions were compared by χ^2 tests. All statistical cal-

Figure 1. Mean Doses of Clozapine in the Discharge Time After First and Last Remission in the Study Group Versus Control Group



*Paired t test; t = 3.5, df = 55, p < .001.

Figure 2. Delta of Mean Clozapine Dose From the Start to the End of the Study



*t = 3.5, df = 55, p < .001.

culations were performed with Statistica software, version 7.0 (StatSoft Inc., Tulsa, Okla.).

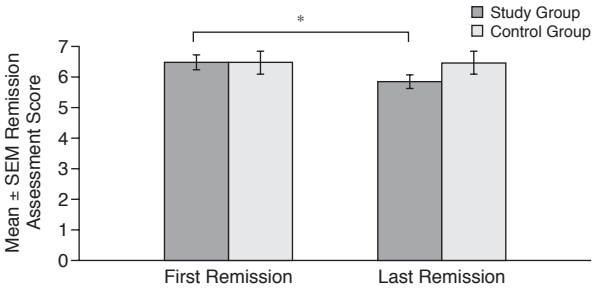
In order to calculate the mean percent change of clozapine dose, we evaluated the percentage delta for each individual. We used the following formula: percent change of clozapine dose = 100 × [(initial clozapine dose) – (final clozapine dose)/(initial clozapine dose)]. We then determined the mean delta for the entire sample.

RESULTS

The study group consisted of 43 clozapine-treated patients (33 men and 10 women) who suddenly stopped the treatment and were rehospitalized due to acute psychotic exacerbation. All were retreated with clozapine. The control group included 12 clozapine-treated patients (7 men and 5 women) who continued the same dose of clozapine without interruption.

The percentage of women among the compliant patients (the control group) was twice as high as among the noncompliant patients (the study group) (41.7% vs. 23.3%, respectively). There were no demographic differences between the groups in terms of age and diagnoses (Table 1).

Figure 3. Quality of Remission of the First Discharge From the Hospital Versus the Final Condition for the Study Group and the Control Group



*t = 2.07, df = 74, p < .05.

Mean ± SEM doses of clozapine at discharge after the first remission were similar for both groups: 358.4 ± 21.5 mg/day for the study group and 365.6 ± 55.7 mg/day for the control group (p > .5). However, there was a significant difference within the study group when comparing the initial (358.4 ± 21.5 mg/day) and final (461.6 ± 20.2 mg/day) doses (t = 3.5, df = 55, p < .001) (Figure 1). The change in the dose of clozapine from the first to the last remission expressed as a percentage (Figure 2) shows a significant difference, with a 43% increase in the study group compared with a 12.5% decrease in the control group (t = 3.5, df = 55, p < .001).

Figure 3 demonstrates the comparison of quality of remission scores for both groups between the first remission and the final state. A comparison of each of the 3 components separately did not demonstrate significant differences. However, the total remission score (the summary of 3 components together) showed a deterioration in the study group (mean ± SEM: 6.5 ± 0.2 vs. 5.8 ± 0.2; t = 2.07, df = 74, p < .05), while the remission score in the control group did not show any change.

DISCUSSION

Although there were some interesting and positive findings in our study, we would like to mention some of its limitations. This was a retrospective study with a relatively small number of patients, and our conclusions are thus restricted. As a retrospective study, the main problem in designing the research protocol was the absence of standard scales for assessment of the mental state and the quality of remission. For this reason, we had to collect the data from each file and combine them into an assessment score. The possibility should be considered that the clinician who treated the patient the second time may have used different criteria for adjusting the dose. One could suppose that the physician was aware of the evidence that higher doses are needed after abrupt withdrawal. How-

ever, this assumption can be rejected by the fact that clozapine is a carefully monitored medication, and its dose is increased very slowly according to the patient's condition, and clozapine retreatment is started from a minimal dose.

It should be mentioned that the whole sample, both the study and control groups, included chronic, treatment-resistant patients who were hospitalized for a few years until starting clozapine treatment. This situation gave us the opportunity to discharge them from the hospital when they achieved the maximum remission. However, since patients with psychotic exacerbation were readmitted from the community, we had no exact data regarding the length of time on clozapine before discontinuation, a fact that did not let us compare these data to the period of time until the first remission with the medication. Further independent prospective studies performed on larger samples are needed to confirm or reject our findings, using standard assessment scales such as the Global Assessment of Functioning, the Brief Psychiatric Rating Scale, the Scale for the Assessment of Negative Symptoms, or the Positive and Negative Syndrome Scale.

Our retrospective rating study showed a significant difference between the starting and final mean doses of clozapine. Those patients who stopped the clozapine treatment needed greater doses of clozapine in order to achieve a new remission, in contrast to the patients who continued their treatment. It is important to emphasize that the control group demonstrated a trend toward reduction in the clozapine final dose. In addition to these findings, the study showed that there was a significant difference between the 2 groups' quality of remission. The study group demonstrated deterioration in the total remission score, in contrast to the control group, who returned to baseline level and showed no further change in quality of remission.

Our findings regarding patients' level of function correspond with the results of other reports that support the effectiveness of compliance in improving function and continuing residence in the community after psychotic exacerbations.[26]

We think that even though our results are preliminary, they suggest a possible direction of thought concerning practical implications of patient compliance in the prevention of relapses due to cessation of clozapine treatment. Clozapine as an atypical antipsychotic has minimum extrapyramidal side effects, which thus helps to improve treatment compliance and prevent relapse.[27] Zita and Goethe[28] concluded that the drug is most successful when taken as prescribed and that clozapine support groups may help to advance the goals of collaboration and recovery.

In regard to the issue of therapeutic tolerance, rebound psychosis, and supersensitivity psychosis, it must be said that giving the drug only once daily may reduce these phenomena, as opposed to giving multiple doses that may initially enhance D_2 receptor down-regulation but then cause increased receptor density.

This study suggests that the discontinuation of clozapine treatment leads to a deterioration in the quality of remission, with a need for an increased dose of clozapine. Further prospective studies on larger samples are needed to confirm these findings.

Drug names: clozapine (Clozaril, FazaClo, and others), olanzapine (Zyprexa), quetiapine (Seroquel).

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